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An analysis of the University Group Diabetes Study Program:

Data results and conclusions

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The University Group Diabetes Program (UGDP) study, published in *Diabetes*, the journal of the American Diabetes Association (19: 747-830, 1970), constitutes one of the most substantial epidemiological studies ever undertaken. Its purpose was to study the therapeutic effect of certain oral agents, principally tolbutamide, on the degenerative sequelae of mild diabetes mellitus. In order to accomplish geographical diversification and to enlist quickly a sufficient number of suitable diabetic patients, the program was divided among 12 university clinics across the United States. All the professional participants were well qualified, and a supervisory executive body with appropriate committees ensured that a uniformly high standard of practice obtained. Four biostatistical methods were applied to the data, namely, chi squares tests of significance, Monte Carlo monitoring procedure, likelihood approach, and multiple regression analysis with a logistic modification by Cornfeld.

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Mortality results

In the group which comprised tolbutamide-treated patients there were 26 cardiovascular deaths compared to 10 such deaths in the placebo group of 205 patients, during the eight-year study period. This difference was highly significant according to every statistical method applied, and is convincingly enunciated in the above publication.

UGDP conclusions

The American Diabetes Association and the American Medical Association carefully examined the UGDP data and conclusions, and lent their official support to the decision that the administration of tolbutamide results in an increased mortality rate due to cardiovascular causes. The Federal Drug Administration in the

U.S.A. followed with a circular letter to the medical profession, warning physicians of the hazards of this type of therapy, and giving advice on the clinical treatment of diabetes mellitus.

Impact and questions

Unfortunately, all of this occurred prior to the publication of the UGDP report, and appeared sensationally in the news media more than six months before the report was issued. The impact upon both the lay public and the medical profession was extreme. Having just endured the somewhat frivolous threat of cancer caused by cyclamates in their food, diabetics were now told that they were being exposed to an increased likelihood of death from heart disease. Losing confidence in their physicians, some patients who were dependent upon oral hypoglycemic agents for diabetic control abandoned these without seeking a medical consultation. Clinicians, too, wondered about these claims, and although their individual experience could not compare with the combined resources of the UGDP, were they to accept their conclusions as a dictum, or bravely to carry on until the opportunity for analyses became available? If the doctor did continue such practice, was he legally liable for deaths due to heart disease after having been warned about these drug risks? Were responsible pharmaceutical companies producing a lethal agent? In any case, the reputation of their product would always be tarnished, and was this justifiable? Should life-insurance companies reappraise clients who were receiving oral therapy and decline such risks in the future? How could tolbutamide, which makes more endogenous insulin available to the organism, result in an increased number of cardiac deaths? Above all, are the conclusions of UGDP tenable? Are we entering an era of syndicated science which has become unassailable, especially by the individual?

Arbitrary diagnosis

The diagnosis of diabetes in patients selected for the UGDP study was based on the oral glucose tolerance test, and those patients with the sum of blood sugar values at 0, 1, 2 and 3 hours equal to or greater than 500 were classified as diabetics. This method of assessment is by its nature arbitrary and allows the inclusion of cases that would be rejected as non-diabetic by other criteria. For example, 24% of the UGDP cases would not have been acceptable by the Wilkerson System, and 6% would not have satisfied the Fajans and Conn specifications.

The glucose tolerance curve is the result of a combination of factors governing gastrointestinal absorption, intermediary metabolism of fat, protein and glucose, and the peripheral utilization of glucose, all of which may be modified by age and disease. With approximately 60% of the subjects over 50 years of age at the time of enrolment, and 46% already suffering from one or more cardiovascular risk factors, it is doubtful whether the sum GTT was a valid method of diagnosing diabetes for this kind of study. It would have been preferable to select clinically overt diabetics with significant fasting hyperglycemia or unequivocally raised results from the glucose-tolerance tests.

"Mild" diabetes

A second criterion for selection required that the patient subsist on diet alone for one month without developing ketoacidosis or "major diabetic symptoms". It is common experience for adult-onset diabetics to become symptom-free and remain non-ketotic as a result of minor dietary restriction. This observation does not necessarily classify these patients as "mild" diabetics because their biochemical response may be resistant to all types of treatment, and they may already be suffering from complications of the disease which would label them as severe diabetics. This criticism would not have been necessary had the mild cases been defined as those patients who are free from complications and respond ideally to any of the standard forms of treatment.

"Short" duration

Another rule for patient enrolment was that the diagnosis of the disease must have been made within one year. The degenerative complications of diabetes are a product of the duration of the disease. If the one-year limitation was invoked in order to acquire a preponderance of new diabetics for the study, it failed to do so because, on admission, 46% of the diabetic subjects had cardiovascular risk factors–angina, ECG changes, etc.; 42% had retinal exudates and 16% had retinal hemorrhages, etc.; still others had renal and neurological disease, but the precise number of these is not available.

Heterogeneous baseline

The UGDP erred in the method of selecting mild diabetics for this program. It relied on the ubiquitous sum GTT for diagnosis, one-month survival on diet as evidence of mildness, and less than one year from the date of diagnosis to ensure short duration. Unfortunately this system of admission permitted the inclusion of some doubtful diabetics in the study, as well as many severe and advanced cases with degenerative stigmata of the disease. This procedural method allowed a heterogeneous population to be selected as a baseline for study.

Therapy failure

The purpose of this study was to compare the influence of various types of treatment on the natural history of the disease.

It is evident from Fig. 1 that, apart from a brief initial response, there was consistent therapeutic failure in the three categories of diet, diet and tolbutamide, and diet and fixed insulin dosage. No comparable information is provided for postprandial control which in the maturity-onset diabetic might be expected to have been less complete. It is not reasonable to compare the therapeutic effects of tolbutamide and diet with placebo and diet when therapy in these two groups is obviously ineffective. This clinical defect constitutes a fundamental weakness in the research design of the UGDP study.

Omission of rate of appearance of complications

The principal purpose of this program was to monitor the evolution of the diabetic sequelae in the various

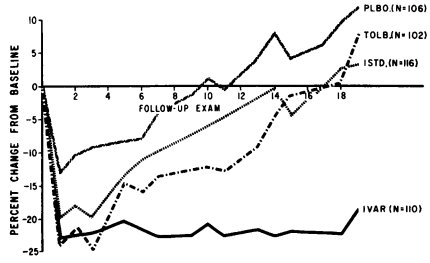

FIG. 1—Percentage of change in fasting blood glucose levels from baseline to each follow-up examination for the cohort of patients followed through 19 examinations.
(Reproduced, with permission of the American Diabetes Association, from the University Group Diabetes Study Program report, published as Volume 19, Supplement 2 of the journal *Diabetes*.)

treatment groups. While such information is not necessary to support the significance of the mortality rates that were eventually observed, nevertheless it would have been useful to those clinicians who are not statistically oriented. These results are not included but their publication is promised.

Failure to obtain homogeneity by diversification

By diversification of this project among 12 clinics, it was intended to achieve more homogeneity of the clinical baseline. Owing to the unsatisfactory criteria for case selection, it is evident that this did not occur, and some clinics contributed significantly more cardiovascular deaths than did others. The Cincinnati and Minneapolis clinics were particularly weighted in this regard. Both the actual number and percentage of deaths according to the various clinics are set forth in Table I, from *Diabetes* (19 [Suppl II] 808, 1971).

Ineffective randomization

By randomizing their patients among the various treatment groups, it was the aim of the UGDP to escape the criticism that variables in the baseline might provoke. The object of this process is to scatter all of the factors equally among the groups, so that only the differences in the treatment were responsible for the results obtained. It may be compared to a card game in which the cards are shuffled carefully and each player is supposed to receive "hands" of equal value; only the difference in players' skills will determine the outcome. Very often this uniformity of distribution does not occur, and a clustering of "good" or "bad" cards takes place. This raises the serious question whether randomization did actually fail in the UGDP project, with cardiovascular risks collecting disproportionately in the tolbutamide group. Only a careful study of each patient entered in the program can satisfactorily answer this contention. Such information is not available to analysts of the project. However, the following information, gleaned from several of their published tables, indicates that the randomizing procedure failed in the UGDP study:

The incidence of patients in the age group 45-64 was 12% more frequent in the tolbutamide than in the placebo group.

The incidence of ECG abnormalities was 30% more frequent.

The incidence of angina pectoris was 40% more frequent.

The incidence of seriously impaired visual acuity was 50% more frequent.

The incidence of serum cholesterol over 300 mg./100 ml. was 90% more frequent.

While the incidence of other modalities was admittedly more prevalent in the placebo group, those listed above would be given serious consideration by a seasoned clinician in pronouncing prognostic judgment, and the fact that they were clustered in the tolbutamide series raises grave doubt concerning the efficacy of randomization in this project.

Table I*

Percentage of deaths by clinic

Cardiovascular causes	Placebo	Tolbutamide	Insulin standard	Insulin variable	No. of deaths
Baltimore	0.0	4.5	0.0	0.0	1
Cincinnati	8.7	31.8	16.7	19.0	17
Cleveland	0.0	5.6	0.0	5.0	2
Minneapolis	9.1	25.0	8.3	8.3	12
New York	13.6	10.0	0.0	0.0	5
Williamson	4.3	13.6	8.7	12.5	9
Birmingham	0.0	18.2	0.0	0.0	2
Boston	6.7	23.5	6.3	6.7	7
Chicago	9.1	0.0	8.3	9.1	3
St. Louis	0.0	0.0	8.3	0.0	1
San Juan	0.0	0.0	7.7	0.0	1
Seattle	0.0	0.0	9.1	0.0	1
All clinics	4.9	12.7	6.2	5.9	61

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Unsuitability of statistical methods

The chi square test for drug effect with a value of 7.88 and P value of .005 clearly indicates a significant increase in mortality in the tolbutamide series of patients as compared to the placebo-treated group. However, it is not a method applicable in this complex situation because it is based on the assumption that the two treatment groups are drawn from an identical population with the same mortality rate, and that only a single difference exists, i.e. the kind of treatment that was used. Obviously with the many demographic, clinical and laboratory variables present in each series, such statistical analysis is unsatisfactory. The same objection applies to the more sophisticated methods, namely the Monte Carlo system and the likelihood approach.

Finally, the UGDP mortality data were analyzed by means of a multiple logistic regression model which takes into account 14 baseline variables listed in the study and supports the conclusion that tolbutamide was responsible for an excessive cardiovascular mortality. In order that this statistical approach may be valid, each variable must be assigned a value based on prognostic judgment. Unfortunately, this kind of stratification is not possible at the present time because medical science has not progressed to the point where accurate prognostic assessment can be assigned to hypertension as compared to angina pectoris as compared to ECG changes as compared to hypercholesterolemia, etc. Because of the lack of this kind of knowledge, there cannot be meaningful communication between clinical investigator and biostatistician. Misleading conclusions will be the inevitable result.

Conclusion

A careful analysis has been made of the UGDP study reported by *Diabetes*. The conclusion of the study that tolbutamide therapy is attended by an increased risk of cardiovascular death is rejected on the basis of: (a) an inappropriate method of case selection, (b) an inadequate therapeutic regimen, and (c) unsuitable biostatistical techniques.

The extension of the UGDP conclusions to other oral hypoglycemic drugs is unwarranted.